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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040402

Application Number: 09/768,877
Filing Date: January 23, 2001
Appellant(s): POLONSKY ET AL.

Charles P. Landrum
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/10/2003

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

*(2) **Related Appeals and Interferences***

The brief contains a statement indicating that there are no related appeals or interferences.

*(3) **Status of Claims***

The statement of the status of the claims contained in the brief is correct. The brief contains a statement indicating that an amendment under 37 CFR § 1.116 has been filed concurrently with the brief. The amendment after final rejection filed on 12/10/2003 has been entered as it reduces the number of issues on appeal, particularly, some of the grounds of rejections under 35 USC 112, second paragraph. In view of the amendment filed, rejection of claims 18-21 and 54 due to the recitation of "standard profile", and rejection of claim 53 for not further limiting claim 52, are hereby withdrawn. Newly added claims 115-116 are rejected under 35 USC, 112 first and second paragraphs for the same reasons applied to claims 18-21, 49-51 and 53-64. This will be addressed in the Grounds of Rejection section of this Answer. In view of the amendment filed on 12/10/2003, the current status of the claims is as follows: *claims 18-21, 49-51, 53-64, 115-116 are rejected, claims 52 and 114 are objected, and claims 65-113 are withdrawn from consideration.*

*(4) **Status of Amendments After Final***

The brief contains a statement indicating that an amendment under 37 CFR § 1.116 has been filed concurrently with the brief. As indicated above, this amendment has been entered.

*(5) **Summary of Invention***

The summary of invention contained in the brief is substantially correct. However, it includes statements regarding sections of the specification which allegedly provide support to the claimed embodiments. Such statements are appropriately found in the argument's section of the brief and will be addressed in the Response to Arguments section of this Answer.

(6) Issues

The brief contains two sets of issues (A and B) depending on whether the amendment filed concurrently with the brief is entered. As indicated in the Status of the Claims section of the brief, this amendment has been entered. Section VI(A) of the brief describes the issues if the amendment filed concurrently is entered. The appellant's statement of the issues in section VI(A) the brief is correct.

(7) Grouping of Claims

The brief contains statements regarding the grouping of the claims which are relevant to the claims prior to the amendment filed concurrently with the brief. Since the amendment has been entered, these statements have not been considered. With regard to those statements which are relevant to the current claims, the appellant's statements in the brief that certain claims do not stand or fall together are not agreed with for the following reasons.

Appellants submit that claims 18-21, 49, 51, 53-55, and 57-60 do not stand or fall with the other claims relative to the indefiniteness rejection under 35 USC 112, second paragraph based upon the phrase "calpain 10" because only claims 18-21, 49, 51, 53-55, and 57-60 recite the phrase "calpain 10". This statement is not agreed with as claims 50, 56, 61-64 are dependent claims which incorporate all the limitations recited in the claims from which they depend, i.e. claims 49, 55, 60. In addition, claims 50, 56, 61-64 do not recite any additional limitations which would overcome the rejection applied due to the recitation of the term "calpain 10", and Appellants have not presented any additional reason for the separate patentability of these claims from claims 18-21, 49, 51, 53-55, and 57-60. As such, claims 50, 56, 61-64 stand or fall together with claims 18-21, 49, 51, 53-55, 57-60 relative to the indefiniteness rejection under 35 USC 112, second paragraph based upon the recitation of "calpain 10".

Appellants further submit that claims 19 and 53 stand or fall separately from claims 18, 20, 21, 49, 51, 54-55, and 57-60 as they recite additional limitations upon which additional arguments for the definiteness of the claims may be based. This statement is not agreed with for the following reasons.

The polypeptide of SEQ ID NO: 2 contains 672 amino acids and has been disclosed as a protein having calpain-like protease activity. The specification does not disclose amino acids 1-47 of SEQ ID NO: 2 as being responsible for calpain-like protease activity, "calpain 10" activity, or any specific biological activity. Therefore, while there is a structural limitation recited in claims 19 and 53, this structural limitation does not overcome the indefiniteness rejection in view of the fact that it is a small fragment of the polypeptide of SEQ ID NO: 2, there is no teaching as to the function/activity of a polypeptide comprising amino acids 1-47 of SEQ ID NO: 2, and amino acids 1-47 of SEQ ID NO: 2 have not been disclosed as the structural elements in the polypeptide of SEQ ID NO: 2 which is responsible for calpain-like protease activity. Since one of skill in the art cannot determine a function solely on the structural limitation recited, i.e. amino acids 1-47 of SEQ ID NO: 2, and the functional limitation recited, i.e. "calpain 10", is indefinite, one of skill in the art cannot determine the scope of claims 19 and 53. Thus, claims 19 and 53 stand or fall together with claims 18, 20-21, 49-51, 54-64 relative to the 35 USC 112, second paragraph rejection based on the recitation of "calpain 10".

Appellants submit that claims 18-21, 49-51 and 53-64 do not stand or fall with the other claims relative to the written description rejection under 35 USC 112, first paragraph, based on the phrase "calpain 10" because only claims 18-21, 49-51 and 53-64 recite said phrase. This statement is not agreed with as claims 50, 56, 61-64 are dependent claims which incorporate all the limitations recited in the claims from which they depend, i.e. claims 49, 55, 60. As such, claims 50, 56, 61-64 stand or fall together with claims 18-21, 49, 51, 53-55, 57-60 relative to the written description rejection under 35 USC 112, first paragraph based on the recitation of the phrase "calpain 10".

Appellants submit that claims 18-21, 49-51 and 53-64 do not stand or fall with the other claims relative to the lack of enablement rejection under 35 USC 112, first paragraph, based on reference to screening for inhibitors of calpain 10 or amino acids 1-47 of SEQ ID NO: 2 because only claims 18-21, 49-51 and 53-64 refer to screening for inhibitors of calpain 10 or amino acids 1-47 of SEQ ID NO: 2.

This statement is not agreed with as claims 50, 56, 61-64 are dependent claims which incorporate all the limitations recited in the claims from which they depend, i.e. claims 49, 55, 60. As such, claims 50, 56, 61-64 stand or fall together with claims 18-21, 49, 51, 53-55, 57-60 relative to the lack of enablement rejection under 35 USC 112, first paragraph based on reference to screening for inhibitors of calpain 10 or amino acids 1-47 of SEQ ID NO: 2.

(8) Claims Appealed

The brief contains two sets of appealed claims in Appendix A and B depending on whether the amendment filed concurrently with the brief is entered. As indicated in the Status of the Claims section of the brief, this amendment has been entered. Appendix A discloses the claims on appeal if the amendment filed concurrently is entered. The copy of the appealed claims contained in Appendix A of the brief is correct.

(9) Prior Art of Record

Bork , Genome Research, 10:398-400, 2000

Broun et al. , Science 282:1315-1317, 1998

Meyer et al. , Biochem. J. 314:511-519, 1996

Seffernick et al. , J. Bacteriol. 183(8):2405-2410, 2001

Van de Loo et al. , Proc. Natl. Acad. Sci. 92:6743-6747, 1995

Witkowski et al. , Biochemistry 38:11643-11650, 1999

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-21, 49-51, 53-64 remain rejected and newly added claims 115-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

Claims 18-21, 49, 51, 53-55, 57-60, 115 and 116 (claims 50, 56, 61-64 dependent thereon) are indefinite in the recitation of the term "calpain 10" for the following reasons. While the specification discloses that a calpain 10 is an atypical calpain and that it is similar in structural organization to calpain 5 and 6 (page 31, lines 8-11), the specification fails to disclose which are the characteristics which are unique to a polypeptide from any organism having "calpain 10" function such that one of skill in the art could clearly distinguish a calpain 10 from other calpains, particularly 5 and 6. Since there is no disclosure regarding the specific structural and functional characteristics which are associated with calpain 10 polypeptides, one of skill in the art cannot reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112, first paragraph, new matter

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19, 49 and 53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 19 and 53 (claim 49 dependent thereon) encompass a method of screening for a modulator of calpain 10 function wherein the calpain 10 polypeptide used comprises amino acids 1-47 of SEQ ID NO: 2. While the specification discloses a method as described above wherein the calpain 10 polypeptide used is that of SEQ ID NO: 2, the Examiner has been unable to locate adequate support in

the specification for a method of screening for a modulator of calpain 10 function with a calpain 10 polypeptide which comprises specifically amino acids 1-47 of SEQ ID NO: 2. Furthermore, the Examiner has not been able to find a specific reference to amino acids 1-47 of SEQ ID NO: 2. Thus there is no indication that methods using specifically calpain 10 polypeptides which comprise amino acids 1-47 of SEQ ID NO: 2 were within the scope of the invention as conceived by Appellants at the time the application was filed.

Claim Rejections - 35 USC § 112, first paragraph, written description

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-21, 49-51, 53-64 remain rejected and newly added claims 115-116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 18, 19, 20-21, 49, 50, 51, 53 and 54-64 are directed to (1) a method of screening for a modulator of a genus of calpain 10 polypeptides, or (2) a method of screening for a modulator of a genus of calpain 10 polypeptides comprising amino acids 1-47 of SEQ ID NO: 2. Newly added claims 115-116 are directed to a method of screening for a modulator of a genus of human calpain 10 polypeptides.

A sufficient written description of a genus requires that the specification describe the attributes and features of a sufficient number of species within the genus so that the described species are representative of the attributes and features of all members of the genus. A complete description of any species should include description of both the structure and function of the species. While the specification provides the structure of several human polypeptides labeled calpain 10 and one mouse

calpain 10, the species described are not considered sufficient to describe the entire genus of calpain 10 polypeptides required to practice the claimed method. It is worth noting that the human calpain 10 polypeptides disclosed in the specification are splice variants encoded by a single gene, i.e. CAPN10. As it can be seen at least in Figure 1, not all the splice variants disclosed will have the same activity as that of the polypeptide of SEQ ID NO: 2 (Figure 1A, calpain 10A) which is the complete gene product. See for example Figure 1H, where the polypeptide labeled calpain 10H lacks all the domains present in calpain 10A which correlate with the proteolytic activity associated with calpains and only contains domain I and domain T (C-terminal domain). Only one human and one mouse gene have been disclosed as encoding calpain 10 polypeptides and only two completely functional calpain 10 polypeptides have been disclosed. The specification fails to provide the structures of all the calpain 10 polypeptides required in the claimed method, or the structural elements which are common to all calpain 10 proteins from any organism. In addition, the specification fails to disclose which are the critical structural elements in the human and mouse calpain 10 polypeptides disclosed which are required in any polypeptide to display calpain 10 activity. Furthermore, as indicated above, while the specification discloses that a calpain 10 protein is similar in structure to calpain 5 and 6 (page 31, lines 8-11), it does not provide any guidance as to which are the structural elements which are specific to a calpain 10 and are not found in a calpain 5 or 6 such that one of skill in the art would know if a polypeptide is a calpain 10 or a calpain 5 or 6. It is also noted that while the specification discloses the polypeptide of SEQ ID NO: 2 (672 amino acids) as having calpain-like protease activity, the specification fails to disclose a correlation between amino acids 1-47 of the polypeptide of SEQ ID NO: 2 and any biological activity, or if amino acids 1-47 of SEQ ID NO: 2 is all that is required in any polypeptide to display the same activity as that of the polypeptide of SEQ ID NO: 2.

The genus of polypeptides required to practice the claimed method is a large and structurally variable genus. While a sufficient written description of a genus of polypeptides may be achieved by a

recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus., in the instant case, either (1) there is no structural feature which is representative of all the members of the genus of calpain 10 polypeptides recited in claims, or (2) the structural feature recited, i.e. amino acids 1-47 of SEQ ID NO: 2, does not constitute a substantial portion of the genus as the remainder of any polypeptide comprising said structural element is completely undefined and the specification does not define the remaining structural features for the members of the genus to be selected.

Furthermore, while one could argue that the genus of polypeptides required to practice the claimed method is adequately described by the polypeptides disclosed in the specification, since one could use the structures disclosed in the specification and those known in the art to isolate other calpain 10 polypeptides by structural homology, it is noted that the art teaches the unpredictability of using structural homology to accurately determine function and even a high degree of structural homology may not result in functional homology. Bork (Genome Research, 10:398-400, 2000) teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). In regard to examples showing how small structural changes affect function, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform

a hydrolase to a desaturase. The art, as described above, clearly teaches that a genus of polypeptides as the one required to practice the claimed method, cannot be adequately described absent the disclosure of a correlation between structure and function since structural homology alone is not sufficient for accurate determination of function.

Many structurally unrelated polypeptides are encompassed by these claims. The specification only discloses a few species of the genus of polypeptides required to practice the claimed method which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed invention. Therefore, one skilled in the art cannot reasonably conclude that the Appellants had possession of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-21, 49-51, 53-64 remain rejected and newly added claims 115-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for a modulator of the calpain polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a method of screening for inhibitors of (1) any calpain 10 polypeptide, (2) any human calpain 10 polypeptide, or (3) any calpain 10 polypeptide comprising amino acids 1-47 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *In re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6)

the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The instant claims are directed to a method of screening for a modulator of any calpain 10 polypeptide, any human calpain 10 polypeptide, or any calpain 10 polypeptide comprising amino acids 1-47 of SEQ ID NO: 2. The scope of the claims is not commensurate with the enablement provided in regard to the large number of unknown calpain 10 polypeptides required to practice the claimed method. While the specification provides the structure of several human splice variants encoded by a single gene, i.e. CAPN10, and one mouse calpain 10, the specification fails to provide (1) the structure of other calpain 10 polypeptides, (2) the structural elements which are common to all calpain 10 proteins from any organism, or (3) the critical structural elements in the human and mouse calpain 10 polypeptides disclosed which are required in any polypeptide to display calpain 10 activity. Furthermore, as indicated above, while the specification discloses that a calpain 10 protein is similar in structure to calpain 5 and 6 (page 31, lines 8-11), it does not provide any guidance as to which are the structural elements which are specific to a calpain 10 and are not found in a calpain 5 or 6, such that one of skill in the art can distinguish between a calpain 10 and a calpain 5 or 6. In addition, while the specification discloses the polypeptide of SEQ ID NO: 2 (672 amino acids) as having calpain-like protease activity, the specification fails to disclose (1) a correlation between amino acids 1-47 of the polypeptide of SEQ ID NO: 2 and any biological activity, including calpain 10 activity, or (2) if amino acids 1-47 of SEQ ID NO: 2 is all that is required in any polypeptide to display the same activity as that of the polypeptide of SEQ ID NO: 2.

The argument can be made that the claimed invention, i.e. method of screening for a modulator of any calpain 10 polypeptide, any human calpain 10 polypeptide, or any calpain 10 polypeptide comprising amino acids 1-47 of SEQ ID NO: 2, is enabled by the teachings of the specification and what is known in the prior art since one could obtain the calpain 10 polypeptides required by the claimed method by sequence comparison using the structures disclosed in the specification and those of the prior art.

However, as previously discussed, the state of the art teaches the unpredictability of accurate determination of function based solely on structural homology. As discussed above, Bork teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Furthermore, the art clearly teaches examples in support of the teachings of Bork which show how small structural changes result in changes in function, therefore indicating that structural homologs may not share a similar function. Witkowski et al. teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art, as described above, clearly teaches that even one amino acid substitution can result in a polypeptide having different function, therefore isolating/making the polypeptides required to practice the claimed method would require undue experimentation absent any teaching as to how structure correlates with calpain 10 function.

Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the structural elements required in any polypeptide to display calpain 10 function, the lack of knowledge as to the structural elements which would allow one of skill in the art to distinguish between a calpain 10 and a calpain 5 or 6, the lack of knowledge as to the structural elements in the calpain 10 polypeptides disclosed in the specification which are also found in other calpain 10 polypeptides from other organisms, and the unpredictability of the art in regard to determining function based solely on structural homology, one of skill in the art would have to go through the burden of undue

experimentation in order to isolate the calpain 10 polypeptides required to practice the claimed method. Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the invention as claimed.

*(11) **Response to Argument***

On page 7 of the Brief, last paragraph and continuing on pages 8-9, Appellants submit a summary of the argument indicating that (1) claims 18-21, 49, 51, 53-55 and 57-60 are definite under 35 USC 112, second paragraph relative to the recitation of "calpain 10", (2) claims 19 and 53 satisfy the written description requirement under 35 USC, first paragraph, as the phrase "amino acids 1-47 of SEQ ID NO: 2" does not introduce new matter, (3) claims 18-21, 49-51 and 53-64 satisfy the written description requirement under 35 USC 112, first paragraph as the phrase "calpain 10" is described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention, and (4) claim 18-21, 49-51, and 53-64 satisfy the enablement requirement under 35 USC 112, first paragraph because the claimed method is described in the specification and enables one of skill in the art to make and/or use the invention commensurate in scope with these claims. Appellants further submit that the Examiner has not presented substantial evidence to support her position that the claims recite terms which render them indefinite, or that the specification fails to adequately describe or enable the claims. Appellant also submit that they have presented overwhelming evidence in the form of citations to particular passages in the specification and to dictionary definitions to show that the claims are not indefinite. Furthermore, Appellants submit that similar evidence has been presented regarding the written description and enablement of the claims at issue.

The Examiner acknowledges the summary of the argument presented. Each of the arguments presented regarding the issues on appeal will be addressed in the order they have been presented in the Arguments section (IX) of the brief.

A. Substantial evidence required to support the Examiner's position on appeal

On page 9 of the brief, last paragraph, and continuing on page 10, Appellants submit that findings of fact and conclusions of law by the USPTO must be made in accordance with the Administrative Procedure Act. Applicants cite *Dickinson v. Zurko*, 527 US 150, 158 (1999) and *In re Gartside*, 203 F.3d 1305, 1314-1315 (Fed. Cir. 2000) in support of the argument that the Examiner's position on appeal must be supported by substantial evidence within the record in order to be upheld by the Board of Patent Appeals and Interferences. According to Appellants, the Examiner has not put forth "substantial evidence" that the presently appealed claims are indefinite, whereas in contrast, Appellants have provided strong evidence in the form of citations and definition of terms in the specification to show that the instant claims are definite.

The Examiner acknowledges the findings in *Dickinson v. Zurko*, 527 US 150, 158 (1999) and *In re Gartside*, 203 F.3d 1305, 1314-1315 (Fed. Cir. 2000), as well as a copy of the definition of the term "standard" as published in Webster's New Twentieth Century Dictionary of the English Language, second edition, provided with the brief. It is noted that in view of the amendment filed concurrently with the brief, the term "standard" is no longer recited. As such, arguments regarding submission of substantial evidence as they relate to the term "standard" are now moot. However, the Examiner disagrees with Applicant's contention that the Examiner's position in regard to the issues on appeal is not supported by substantial evidence within the record in order to be upheld by the Board of Patent Appeals and Interferences. The Examiner will address arguments in regard to the indefiniteness of the claims and the evidence presented by the Examiner and Appellants as follows.

B. Claim rejections under 35 USC § 112, second paragraph

1. Claims 18-21 and 54 are allegedly definite

On page 10 of the Brief, Appellants assert that claims 18-21 and 54 are definite in regard to the recitation of "standard activity profile". Appellants argue that according to the Webster's Dictionary, the definition of standard is "something established for use as a rule or basis of comparison in measuring or judging capacity, quantity, content, extent, value, quality, etc.". Furthermore, Appellants argue that the specification at page 7, lines 17-19, clearly provides an example of determining a standard activity profile.

First, it is noted that claims 18-21, 54 and 114 were previously rejected due to the recitation of "standard activity profile" as indicated in the Final Action mailed on 3/26/2003, page 3, paragraph 6. It is noted that as indicated by the definition of "standard" in the Webster's Dictionary, a standard is something established for use as a rule or basis of comparison. Therefore, unless this standard is established or defined in the specification, one of skill in the art would not know what a "standard activity profile" is. An enzyme activity profile will be different depending on the conditions chosen to measure such activity, e.g. substrate, temperature, pH, etc. Furthermore, the specification at page 7, lines 17-19, does not define the term "standard" as it relates to the activity profile of a calpain 10. Thus, the term "standard activity profile" as previously recited in the claims is indefinite. However, in view of the amendment filed, the rejection of claims 18-21, 54 and 114 under 35 USC 112, second paragraph due to the recitation of the term "standard activity profile" is hereby withdrawn since the amended claims no longer recite the term "standard activity profile".

2. Claims 18-21, 49, 51, 53-55 and 57-60 are allegedly definite

On page 11 of the brief and continuing on page 12, Appellants argue that claims 18-21 and 54 are definite. In particular, Appellants refer to page 29, line 18 of the specification, where it is indicated that calpain 10 is a novel calpain-like protease. Furthermore, Appellants submit that one of skill in the art would understand the term "calpain 10" in light of the specification, pages 5-8, page 18, pages 29-32,

pages 37-38, pages 87-94, Figures 1 and 5, and the sequence listing, which provides the sequences of various isoforms of calpain 10. Appellants assert that Figure 1 discloses the structure of calpain 10 and given the description of methods used to identify the mouse homolog of calpain 10, one would readily be able to identify homologs of the gene by sequence and structural comparisons. According to Appellants, one of skill in the art would be able to differentiate and/or identify a calpain 10 from a calpain 5 or 6 by any of a variety of sequence analysis methods available in the art. It is Appellant's contention that the Examiner provides no evidence to the contrary and that the breadth of the claims should not be equated with indefiniteness.

For the record, it is noted that claims 18-21, 49-51, 53-64, and newly added claims 115-116 have been rejected under 35 USC 112 second paragraph due to the recitation of "calpain 10". The Examiner acknowledges the teachings of the specification and agrees with Applicant's contention that breadth should not be equated with indefiniteness. However the Examiner disagrees with Appellant's contention that (1) one of skill in the art would readily understand the term "calpain 10", or (2) the Examiner has not provided evidence to show that one of skill in the art would not know what the term "calpain 10" encompasses. While it is agreed that the human and mouse polypeptides disclosed in the specification appear to have calpain activity and they have been disclosed as "calpain-like proteases", the term "calpain 10" as an indicator of function is indefinite absent a description of the specific structural and/or functional characteristics specifically associated with any calpain 10 polypeptide not shared by other calpains, such that one of skill in the art would know which polypeptides are encompassed by the claims. This is particularly evidenced, as indicated by the Examiner in the Final Action mailed on 3/26/2003, by the teachings of the specification which discloses that a calpain 10 is an atypical calpain and that it is similar in structural organization to calpain 5 and 6 (page 31, lines 8-11). The specification completely fails to disclose which are the structural/functional characteristics which are unique to a polypeptide from any organism having "calpain 10" function such that one of skill in the art could clearly distinguish a calpain

10 from other calpains, particularly 5 and 6. Furthermore, Appellants have presented no evidence which would indicate that one of skill in the art would know how to distinguish a calpain 10 from a calpain 5 or 6, other than to indicate that one of skill in the art can use a variety of sequence analysis methods available. It is worth noting that the specification fails to disclose (1) which are the structural elements which would allow one to differentiate a calpain 10 from a calpain 5 or 6, (2) which are the structural elements in the human and mouse polypeptides disclosed which would allow one of skill in the art to recognize a calpain 10 from any organism, or (3) the level of structural homology shared between the human and mouse polypeptides disclosed and any calpain 10 polypeptide such that one of skill in the art would recognize and/or identify a calpain 10 from any organism. In the absence of information regarding the structural elements which are specific to calpain 10 or the level of structural homology between the polypeptides disclosed and any calpain 10, it is unclear as to how one of skill in the art can use a variety of sequence analysis methods to differentiate and/or identify any calpain 10 polypeptide. While it is clear from the specification that the term "calpain 10" is intended to encompass the specifically disclosed species (i.e. SEQ ID NO: 2 and the splice variants encoded by the CAPN10 gene), it is also clear that Appellants intend the term to be broader than simply these specific species. What is not clear is how the skilled artisan recognizes which polypeptides which are not identical to the disclosed species are also within the scope of the term "calpain 10" and which might be "calpain 5", "calpain 6" or even be a new subclass of calpains altogether. The metes and bounds of the term "calpain 10" are entirely unclear from the specification. Thus, in view of the evidence presented, the teachings of the specification, the lack of a specific definition for the term "calpain 10", and the lack of information as to which are the specific structural/functional characteristics shared only by calpain 10 polypeptides, one cannot reasonably conclude that the term "calpain 10" as recited in the claims is definite.

3. Claim 53 is allegedly definite upon entry of the amendment after final

In view of the entry of the amendment filed concurrently with the brief, claim 53 no longer recites "claim 52". Thus, this rejection is hereby withdrawn.

C. Claim rejections under 35 USC § 112, first paragraph

On page 12, and continuing on page 12, Appellants traverse the written description rejections under 35 USC 112, first paragraph of claims and indicate that they submit evidence which shows Appellants were in possession of the claimed invention at the time of the fling of the present application. Appellants cite Vas-Cath Inc. v. Mahurkar 19 U.S.P.Q.2d 1111,1117 (Fed.Cir.1991) and indicate that possession of the invention is shown by describing all its claimed limitations and not that which is obvious. Appellants further cite MPEP 2163, *Lockwood v. American Airlines, Inc*, 107 F.3d l 565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997), *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *University of California v. Eli Lilly and Co.* (CA FC) 43 USPQ2d at 1406, and *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) to indicate that possession of the claimed invention can be shown by describing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention.

The Examiner acknowledges the case law provided by Appellants and agrees that (1) describing that which is well known in the art is not required to show possession of the claimed invention, and (2) possession of the claimed invention can be shown by describing identifying characteristics sufficient to show possession of the claimed invention. However, the Examiner disagrees with Appellant's contention that the claimed invention complies with the written description requirement of 35 USC 112, first paragraph and will address the arguments presented in the following paragraphs.

1. Claims 19 and 53 allegedly satisfy the 35 USC § 112, first paragraph written description requirement

On page 13 of the specification, and continuing on page 14, Appellants submit that the phrase "amino acids 1-47 of SEQ ID NO: 2" is described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Appellants refer to page 29, line 24 and assert that a coding region of exon 1 of calpain 10 is described as nucleotides 1375-1515. It is Appellant's contention that one of ordinary skill in the art would readily recognize the relationship between nucleic acid coding region and amino acid sequence, as exemplified in Table 4 (page 58). Thus, according to Appellants, one of ordinary skill in the art would recognize that the coding region of exon 1 corresponds to amino acids 1-47 of calpain 10, and assert that description of amino acids 1-47 of SEQ ID NO: 2 can be found at least on page 29, line 24.

For the record, it is noted that claims 19, 49 and 53 have been rejected under 35 USC 112, first paragraph for containing new matter. Claims 19 and 53 were amended in response to the first Office Action on the merits mailed on 10/16/2002, to recite "amino acids 1-47 of SEQ ID NO: 2". While the Examiner agrees that (1) page 29, line 24 describes the nucleotides within SEQ ID NO: 1 which correspond to exon 1 as well as which nucleotides within exon 1 correspond to the coding region, and (2) nucleotides 1375-1515 of SEQ ID NO: 1, which are disclosed in the specification as being the coding region of exon 1, encode amino acids 1-47 of SEQ ID NO: 2, the specification does not disclose practicing the claimed method specifically with the genus of polypeptides which comprise this fragment of SEQ ID NO: 2 (amino acids 1-47) as a preferred embodiment nor does it disclose this fragment of SEQ ID NO: 2 as one which identifies proteins having calpain 10 activity such that one could use it as a method for screening for modulators of calpain 10 function, as recited in the claims. Appellants have not indicated which section of the specification discloses practicing the claimed method with a polypeptide comprising amino acids 1-47 of SEQ ID NO: 2 as a preferred embodiment. Thus, there is no indication that methods using specifically calpain 10 polypeptides comprising amino acids 1-47 of SEQ ID NO: 2 were conceived by Appellants at the time the application was filed.

2. Claims 18-21, 49-51 and 53-64 allegedly satisfy the 35 USC § 112, first paragraph written description requirement.

On page 14 of the brief and continuing on page 15, Appellants assert that at page 29, lines 18-30 and pages 30-31, they have provided more than adequate description of calpain 10. According to Appellants, Figures 1 and 5, as well as SEQ ID NO: 2, disclose an exemplary full length calpain 10 and its various exon regions which are differentially spliced to create different calpain 10 isomers. Appellants also refer to Table 1 which describe calpain 10 isoforms and page 31 of the specification as disclosing a structural description of the domains of calpain 10. Appellants submit that Figure 6 provides a phylogenic tree of the calpain large subunit and that pages 26, 148, 149 as well as Example 8 disclose that calpains are a family of structurally related intracellular multidomain cysteine proteinases containing a papain-related catalytic domain, whose activity depends on calcium. In addition, Appellants submit that the sequence listing provides several amino acid sequences corresponding to calpain 10 and its isoforms. It is Appellant's contention that in view of the description provided, it would be clear to one of skill in the art that Appellants had possession of the claimed invention at the time of filing.

For the record, it is noted that claims 18-21, 49-51, 53-64, and newly added claims 115-116 have been rejected under 35 USC 112 first paragraph for lack of written description of the genus of calpain 10 polypeptides, human calpain 10 polypeptides, and calpain 10 polypeptides comprising amino acids 1-47 of SEQ ID NO: 2 required to practice the claimed method. The Examiner acknowledges the teachings of the specification regarding (1) a human gene labeled CAPN10, (2) the structure of said human gene, (3) the structure of several human splice variants encoded by said gene, (4) the structure of a single mouse calpain 10 polypeptide, (5) the different domains commonly found in calpain polypeptides, (6) the sequence listing, and (6) Figures 1, 5, 6 and Table 1. However, the Examiner disagrees with Appellant's

contention that the teachings of the specification provide sufficient description such that it would be clear to one of skill in the art that Appellants had possession of the claimed invention at the time of filing.

A sufficient written description of a genus requires that the specification describe the attributes and features of a sufficient number of species within the genus so that the described species are representative of the attributes and features of all members of the genus. In the instant case, it is reiterated that the specification fails to provide either the structures of all the calpain 10 polypeptides required in the claimed method, or the structural elements which are common to all calpain 10 proteins from any organism, such that the skilled artisan could recognize or visualize other species within the claimed genus. The human calpain 10 polypeptides disclosed in the specification are splice variants encoded by a single gene, i.e. CAPN10. As shown in Figure 1, not all the splice variants disclosed will have the same activity as that of the polypeptide of SEQ ID NO: 2 (Figure 1A, calpain 10A) which is the complete gene product. See, for example Figure 1H, where the polypeptide labeled calpain 10H lacks all the domains present in calpain 10A which correlate with the proteolytic activity associated with calpains and only contains domain I and domain T (C-terminal domain). It should be noted that proteolytic activity is required for the claimed methods. Only one human and one mouse gene have been disclosed as encoding calpain 10 polypeptides and only two completely functional calpain 10 polypeptides are known. In addition, the specification fails to disclose which are the critical structural elements in the human and mouse calpain 10 polypeptides disclosed which are required in any polypeptide to display calpain 10 activity. Furthermore, as indicated above, while the specification discloses that a calpain 10 protein is similar in structure to calpain 5 and 6 (page 31, lines 8-11), it does not provide any guidance as to which are the structural elements which are specific to a calpain 10 and are not found in a calpain 5 or 6 such that one of skill in the art would know if a polypeptide is a calpain 10 or a calpain 5 or 6. It is also noted that while the specification discloses the polypeptide of SEQ ID NO: 2 (672 amino acids) as having calpain-like protease activity, the specification fails to disclose a correlation between amino acids

1-47 of the polypeptide of SEQ ID NO: 2 and any biological activity, or if amino acids 1-47 of SEQ ID NO: 2 is all that is required in any polypeptide to display the same activity as that of the polypeptide of SEQ ID NO: 2.

The genus of polypeptides required to practice the claimed method is a large and structurally variable genus. While a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus., in the instant case, either (1) there is no structural feature recited which is representative of all the members of the genus of calpain 10 polypeptides, or (2) the structural feature recited, i.e. amino acids 1-47 of SEQ ID NO: 2, does not constitute a substantial portion of the genus as the remainder of any polypeptide comprising said structural element is completely undefined and the specification does not define the remaining structural features for the members of the genus to be selected (claims 19 and 53). Thus, one of skill in the art cannot reasonably conclude that the specification describes identifying characteristics sufficient to show that the inventors were in possession of the claimed invention at the time of filing.

On page 15 of the brief, and continuing on pages 16-17, Appellants submit that the references cited by the Examiner are irrelevant in regard to a method for screening for a modulator of calpain 10. According to Appellants, the reasoning provided by the Examiner does not address the currently claimed method. It is Appellant's opinion that the Examiner provides references to support the alteration of enzymatic activities of metabolic enzymes that are in no way related to the calpain 10 polypeptide. With regard to Bork (Genome Research, 10:398-400, 2000), Appellants submit that this reference is concerned with high-throughput screening and prediction of functional and structural characteristics of genes, therefore, it is irrelevant to a method of screening for modulators of calpain 10. With regard to Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), Appellants submit that this reference is concerned

with identifying a fatty acyl desaturase homolog, therefore the percent homology between a new oleate 12-hydroxylase and a known oleate desaturase is irrelevant to a method of screening for a modulator of calpain 10. With regard to Broun et al. (Science 282:1315-1317, 1998), it is Appellant's opinion that the reference addresses the catalytic plasticity of fatty acid modifying enzymes of plants and thus has no relevance to a method of screening for a modulator of a calpain 10 polypeptide. With regard to Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001), Appellants submit that the instant reference addresses the identification of an adaptive alteration in a bacterial enzyme and that this reference teaches the results to be highly exceptional. Therefore, the teachings of Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) et al. are, according to Appellants, irrelevant to methods of screening for modulators of a calpain 10 polypeptide. With regard to Witkowski et al. (Biochemistry 38:11643-11650, 1999) et al., Appellants assert that the instant reference addresses the enzymatic effects of an alteration in a β-ketoacyl synthase, thus not relevant to a method of screening for a modulator of calpain 10.

The Examiner completely disagrees with Appellant's contention that the teachings of Bork, Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. are irrelevant to the issue of written description as applied in the instant case. The Examiner agrees that none of these references teach or suggest a method of screening for modulators of calpain 10 polypeptides. The instant references were introduced by the Examiner to clearly indicate that the deficiencies found in the specification regarding an adequate written description of the genus of polypeptides required to practice the claimed method are not in any way cured by the teachings of the art. Specifically, as indicated in the previous Office Actions and above, the art as evidenced by the teachings of Bork, Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al., clearly teaches that the use of structural homology alone to isolate functional homologs is unpredictable. Bork (Genome Research, 10:398-400, 2000) teaches the general state of the art regarding the unpredictability of assigning function based solely on structural homology. Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. are specific examples which show how

enzymatic activity can drastically change even with small structural changes. Thus, the art, as described above, clearly teaches that a genus of polypeptides as the one required to practice the claimed method, cannot be adequately described absent the disclosure of a correlation between structure and function since structural homology alone is not sufficient for accurate determination of function.

3. Claims 18-21, 49-51, and 53-64 allegedly satisfy the 35 USC § 112, first paragraph enablement requirement

On page 17 of the brief and continuing on page 18, Appellants assert that at page 29, lines 18-30 and pages 30-31, they have provided ample teaching with respect to a calpain 10 and submit that these pages disclose the full length of calpain 10 and its various exon regions that are differentially spliced to create different calpain 10 isomers. Appellants also refer to Table 1 as describing calpain 10 isoforms, the full length of calpain 10, and the sequences corresponding to the SEQ ID NOs. Appellants submit that Figure 1 discloses the alternative spliced forms of calpain 10 indicating the various domains. Furthermore, Appellants submit that Figure 5 discloses an alignment of calpain 10 and various calpains. According to Appellants, page 31 discloses a structural description of the domains of calpain 10 and submit that the specification provides examples which clearly describe how to make and use the claimed invention. In addition, Appellants submit that the sequence listing provides several amino acid sequences corresponding to calpain 10 and its isoforms. Appellants also submit that they have provided relevant teachings to identify characteristics and functionality of calpain 10 and its isoforms, as well as the cloning and localization of calpain 10. Appellants argue that the Examples in the specification have provided the use of calpain 10 in detecting and analyzing polymorphisms in individuals. Thus, it is Appellant's contention that the enablement requirement is met and that they have provided evidence which makes moot the rejection of the claims as lacking enablement.

For the record, it is noted that claims 18-21, 49-51, 53-64, and newly added claims 115-116 have been rejected under 35 USC 112 first paragraph for lack of enablement of the genus of calpain 10 polypeptides, human calpain 10 polypeptides, and calpain 10 polypeptides comprising amino acids 1-47 of SEQ ID NO: 2 required to practice the claimed method.

The Examiner acknowledges the teachings of the specification regarding (1) a human gene labeled CAPN10, (2) the structure of said human gene, (3) the structure of several human splice variants encoded by said gene, (4) the structure of a single mouse calpain 10 polypeptide, (5) the different domains commonly found in calpain polypeptides, (6) the sequence listing, (6) Figures 1, 5 and Table 1, (7) the examples provided, and (8) the association of certain polymorphisms in the human CAPN10 gene and disease. However, the Examiner disagrees with Appellant's contention that the teachings of the specification provide sufficient enablement for the full scope of the claims such that one of skill in the art would not have to go through the burden of undue experimentation to practice the claimed method.

It is reiterated that the scope of the claims is not commensurate with the enablement provided in regard to the large number of unknown calpain 10 polypeptides required to practice the claimed method. While it is agreed that the specification provides the structure of several human splice variants encoded by a single calpain 10 gene, i.e. CAPN10, and one mouse calpain 10, the specification fails to provide (1) other calpain 10 polypeptides, (2) the structural elements which are common to all calpain 10 proteins from any organism, or (3) the critical structural elements in the human and mouse calpain 10 polypeptides disclosed which are required in any polypeptide to display calpain 10 activity. As indicated above, while the specification discloses that a calpain 10 protein is similar in structure to calpain 5 and 6 (page 31, lines 8-11), it does not provide any guidance as to which are the structural elements which are specific to a calpain 10 and are not found in a calpain 5 or 6, such that one of skill in the art can distinguish between a calpain 10 and a calpain 5 or 6. In addition, while the specification discloses the polypeptide of SEQ ID NO: 2 (672 amino acids; calpain 10A) as having calpain-like protease activity, the specification fails to

disclose (1) a correlation between amino acids 1-47 of the polypeptide of SEQ ID NO: 2 and any biological activity, including calpain 10 activity, or (2) if amino acids 1-47 of SEQ ID NO: 2 is all that is required in any polypeptide to display the same activity as that of the polypeptide of SEQ ID NO: 2. It is worth noting that based on Figure 1, it is very unlikely that amino acids 1-47 of SEQ ID NO: 2 are responsible for calpain 10 activity in view of the fact that amino acids 1-41 do not correspond to the domains responsible for proteolytic activity characteristic of calpains in general.

As indicated above and the previous Office Actions, while one could argue that the claimed invention is enabled by the teachings of the specification and what is known in the art since one could obtain the required calpain 10 polypeptides by sequence comparison using the structures disclosed in the specification and those of the prior art, the art as evidenced by Bork, Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. clearly indicates that isolation of functional homologs based solely on structural homology is highly unpredictable. Bork teaches the general state of the art regarding the unpredictability of assigning function based solely on structural homology. Broun et al., Van de Loo et al., Seffernick et al., and Witkowski et al. are specific examples which show how enzymatic activity can drastically change even with small structural changes. The art, as described above, clearly teaches that even one amino acid substitution can result in a polypeptide having different function, therefore isolating/making the polypeptides required to practice the claimed method would require undue experimentation absent any teaching as to how structure correlates with calpain 10 function.

Therefore, in view of the lack of relevant examples, the amount of information provided, the lack of knowledge about (1) the structural elements required in any polypeptide to display calpain 10 function, (2) the structural elements which would allow one of skill in the art to distinguish between a calpain 10 and a calpain 5 or 6, (3) the structural elements in the calpain 10 polypeptides disclosed in the specification which are also found in other calpain 10 polypeptides from other organisms, and the unpredictability of the art in regard to determining function based solely on structural homology, one of

skill in the art would have to go through the burden of undue experimentation in order to isolate/make the calpain 10 polypeptides required to practice the claimed method. Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the invention as claimed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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